REMARKS

Status of Claims

This Preliminary Amendment places the claims in the form they would have been had the Office entered the Amendment After Final, filed February 21, 2002.

In the Final Office Action, the Office indicated that claims 1-24 and 28-30 were pending, and that claims 26 and 27 were withdrawn from consideration. The Office rejected claims 1-24 and 28-30. By the present Amendment, claims 2, 9, 26, and 27 are canceled, claims 1, 3-8, 10-25, and 28-30 are amended, and new claims 31-42 are added. Thus, claims 1, 3-8, 10-25, and 28-42 are pending following entry of this amendment.

Amendment to Specification

The amendment to the specification at page 40 corrects typographical errors in the legend for the data shown in Figures 1 and 2. Prior to correction, the legend on page 40 miscorrelated the results shown in the Figures with the specific Examples that generated those results. The present amendment corrects the previous errors, and the legend now correctly correlates the data in the Figure with the specific Example from which the data came.

Applicants respectfully submit that this correction does not add new matter. The Examples in the specification were performed and produced the data shown in Figures 1 and 2, yet the specific examples from which the data was obtained were mislabeled in the Figures. Because the results of the Examples are reproducible, one of ordinary skill in the art would immediately recognize the proper correlation of Examples with data, and would immediately recognize Applicants' typographical error on page 40. Thus, this

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amendment finds support in the original disclosure provided by the examples, and no new matter is added. Accordingly, Applicants respectfully request entry of the foregoing amendments to the specification.

Amendments to the Claims

Initially, Applicants wish to clarify the record. In the Amendment After Final, filed February 21, 2002, Applicants intended to remove "at least two" from claim 1, in response to suggestions made by the Examiner during a personal interview. However, in the Amendment, Applicants inadvertently left the "at least two" phrase in the claim, yet discussed its absence in their remarks.

In this Preliminary Amendment, given the changed procedural posture, Applicants intend to retain the "at least two" element in claim 1. Applicants respectfully submit that this element is supported throughout the specification, including anywhere the phrase "multiparticulate" is recited. Accordingly, no new matter is added by this amendment.

Claims 1, 3-8, 10-25, and 28-30 are amended, and new claims 31-42 are added by this amendment. Support for these amendments and new claims is found throughout the specification. However, in an attempt to advance prosecution and to assist the Office in evaluating the proposed amendments and new claims, Applicants have identified the following particular passages and sections of the application that provide support for the amendments.

For the element of claim 1 relating to "a bisoprolol plasma concentration of not more than about 1 ng/ml for at least about three hours," attention is directed to page 3, lines 17-20. For the reference to a "sustained release" of the formulation of claim 1,

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attention is directed to the dissolution results shown for Examples 2, 3, 4, and 5 in Figures 1 and 2. For claim 1's recitation of a "therapeutic plasma concentration not later than about 12 hours," and for the "therapeutic plasma concentration for the remainder of a twenty-four hour period," Applicants refer to the plasma concentrations shown in, for example, Figure 3.

Claims 5 and 6, which recite dissolution profiles for the formulations of the instant invention, have been amended to recite that the bisoprolol is "measured" as opposed to "released." These claims are presented in a way that describes the testing conditions under which the claimed dissolution profile occurs. Applicants submit that describing the amounts as being "measured" as opposed to "release" more accurately describes what occurs. The scope of the claim is unchanged by the present amendment, and no new matter is added. These claims are simply clarified by these amendments.

In claims 10 and 11, Applicants have rewritten the claims to replace the terms "major proportion" and "minor proportion" with specific percentages. Support for these amendments is found, for example, at page 10, line 16, through page 12, line 18. Applicants respectfully submit that these amendments clarify these claims, and do not change the scope of these claims.

For new claims 31-34, which recite pH-dependent and pH-independent formulations, Applicants refer the Office to page 11, lines 11-20. For new claim 35, reference is made to the plasma concentrations shown in Figure 3. For claim 36, and its reference to talc, Applicants refer to page 14, lines 13-16. For the recitation of substantially purified forms of bisoprolol in claims 37-39, Applicants refer to page 14,

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lines 20-24. And for the recitation, in new claims 40-42, of different polymers used in the inventive formulation, reference is made to page 12, lines 12-18.

As shown by the foregoing demonstrated support in the as-filed specification, no new matter is presented by any of these amendments or new claims.

Claim Rejection – 35 U.S.C. § 112

In the Final Office Action, the Office rejected claims 10-14 and 28-30 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office alleged that claims 10 and 11 are indefinite for reciting "major portion" and "minor portion," respectively. Claims 12-14 and 28-30 have been alleged to be indefinite for the recitation of "said polymers" or "the or each polymer," each of which the Office states lacks antecedent basis.

In response, Applicants have amended each of the rejected claims to address the rejected terms and more clearly define that which Applicants consider to be their invention. Claims 10 and 11 have been amended to recite a specific percentage of polymer, instead of "major" or "minor" portions. Support for the amendments to claims 10 and 11 can be found, for example, at page 12, lines 12-18. Claims 12-14 and 28-30 have been amended to more clearly define the claimed invention and recite proper antecedent basis. Applicants respectfully submit that these amendments obviate the rejections of record, and thus respectfully request their withdrawal.

Claim Rejections – 35 U.S.C. § 102

In the Final Office Action, the Office rejected claims 1-8, 10-25, and 28-30 under 35 U.S.C. § 102(e) as allegedly anticipated by Busetti et al. (WO 98/32426). The Office

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relies upon Busetti et al. for allegedly anticipating several elements of Applicants' claimed invention. Applicants respectfully traverse this rejection.

Initially, Applicants respectfully note that a proper rejection under 35 U.S.C. § 102(e) can only be made over a U.S. patent or application. Thus, the rejection in the parent application under 35 U.S.C. § 102(e) over Busetti et al. (WO 98/32426) is improper since WO 98/32426 is an International Patent Application publication. However, Applicants note that U.S. Patent No. 6,190,692 B1, which is being filed in an Information Disclosure Statement filed concurrently herewith, is also in the name of Busetti et al., and is believed to be a U.S. counterpart of WO 98/32426.

To be fully responsive to the rejections of record, Applicants now turn to the Examiner's comments regarding WO 98/32426. Applicants respectfully disagree with each of the Office's allegations concerning the disclosure of Busetti et al., and submit that Busetti et al.'s disclosure differs significantly from Applicants' claimed invention. Busetti et al. generically discloses pharmaceutical formulations exhibiting a delayed release. The delay is achieved by coating a core with a swellable polymeric coating, the thickness of which is taught to determine the length of the release delay. Upon expiration of the pre-determined delay time, Busetti et al.'s polymeric coating has completely eroded or dissolved, allowing for a fast dissolution of the core. Busetti et al. provides no teaching for modifying the rate of release following the initial delay/lag, and in fact, emphasizes that the core should rapidly disintegrate following coating dissolution.

For example, Busetti et al. notes that once the lag time has lapsed, "the coating layer should be almost completely dissolved or eroded so that the core should be

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capable of relatively quick disintegration." (Busetti et al., page 12, line 30 to page 13, line 1.) Furthermore, Example 1 results in a dissolution time lag of 302 ± 56 minutes, and a "disintegration time lower than 5 min." for the cores that were coated. Example 3 results in a "dissolution time lag in excess of 300 min., followed by a quick disintegration of the tablet." Example 4 describes how cores having a "disintegration time lower than 5 min." are coated to achieve the desired time lag. Example 5 describes a "disintegration time lag in excess of 300 min." Example 7 describes the coating of cores that "show a disintegration time lower than 5 min. in water," where the disintegration time lag is in excess of 5 hours. In example 8, the results show a "disintegration time lag in excess of 6 hours." Example 9 describes the coating of cores having disintegration times lower than "5 min. in water," where the "disintegration time lag" was in excess of 6 hours. Example 10 describes the results from a coated capsule formulation, in which the "coated capsules showed a dissolution time in excess of 240 min., followed by a quick disintegration of the capsule." Examples 11, 12, 14, and 15 all refer to a "disintegration time lag," and Example 13 refers to a "dissolution time lag."

Even the comparative examples of Busetti et al. describe a delay in release followed by a quick disintegration: Example 2 describes how the "coated tablets show a dissolution time lag in excess of 300 min., followed by a quick disintegration of the tablet;" Example 6 describes a "disintegration time lag in excess of 300 min."

Clearly, Busetti et al. does not teach how to modify the rate of release after the initial time lag. All that Busetti et al. is concerned with is the initial delay in release, and indeed, states the desirability of achieving a very rapid release of the drug in the core. However, such a rapid release of the core contents can result in a spike in plasma drug

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concentration, followed by a decrease over a period of time until the next administration. The ultimate result can be undesirable peaks and valleys in plasma drug concentration over an extended period of dosing.

In contrast, the present invention provides a desired delay in release, but also then provides for a sustained release of the drug from the formulation for a desired period of time. This sustained release period allows for a more gradual introduction of bisoprolol into the body and a more gradual peak in plasma concentration, followed by a more gradual decrease in plasma bisoprolol concentration over the desired dosing period. Over repeated daily use, the present formulation advantageously minimizes peaks and valleys in plasma bisoprolol concentration.

Accordingly, Applicants respectfully submit that the presently claimed invention is not anticipated by the cited Busetti et al. and respectfully request that this rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103

In the Final Office Action, the Office rejected claims 1-8, 10-25, and 28-30 under 35 U.S.C. § 103(a) as being unpatentable over Busetti et al. In response, Applicants respectfully traverse the rejection and submit that Busetti et al. does not render any of the presently pending claims obvious.

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Initially, as noted above, Applicants note that Busetti et al. is not prior art under 35 U.S.C. § 102(e), and thus, cannot be the basis for a rejection under that section of the statute. However, regardless of the statutory basis for the rejection, Applicants submit that Busetti et al. does not render obvious the present invention.

As noted above, Busetti et al. discloses pharmaceutical formulations exhibiting a delayed release. The delay is achieved by coating a core with a swellable polymeric coating, the thickness of which is taught to determine the length of the delay. Upon expiration of the pre-determined delay time, Busetti et al.'s polymeric coating has completely eroded or dissolved, allowing for a fast dissolution of the core. Busetti et al. provides no teaching for modifying the rate of release following the initial delay, and in fact, emphasizes that the core should rapidly disintegrate following coating dissolution.

Furthermore, as noted above, Applicants' claimed invention is directed to a formulation that, following an initial delay in release, provides for a sustained release of bisoprolol over a period of time, thereby affording the maintenance of therapeutic concentrations in the plasma for the remainder of a twenty-four hour period. Thus, a significant difference between Applicants' claimed invention and Busetti et al.'s disclosure is the characteristic drug release following the initial delay: Busetti et al.'s is immediate and fast, whereas Applicants' is gradual and sustained.

Notably, Busetti et al. does not provide any teaching or suggestion as to the possibility, much less the desirability, of a gradual and sustained release following administration. There is nothing in Busetti et al. that would lead one of skill in the art to modify the rate of release of the drug from the core following the dissolution/erosion of the coating. If one were to follow the teachings and suggestions of Busetti et al., one

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would logically seek to *minimize* the time it takes for the core to dissolve. Furthermore, one would seek to optimize the core so as to produce an even quicker dissolution. This is clearly Busetti et al.'s design.

In fact, if one were to follow the teachings and suggestions of Busetti et al., one could not arrive at the present invention. Busetti et al. leads the skilled artisan in the opposite direction of the present invention. Busetti et al. teaches that the cores desirably release their drug component as quickly as possible, whereas the present invention achieves a release of the drug from the formulation that is gradual and sustained. If anything, Busetti et al. teaches away from the present invention and its unobvious advantages. And courts have long recognized that a document that teaches away from a claimed invention cannot render that claimed invention obvious.

In view of the foregoing, Applicants respectfully submit that Busetti et al. does not render the claimed invention obvious, and Applicants accordingly respectfully request the withdrawal of the rejection of claims 1-8, 10-25, and 28-30 under 35 U.S.C. § 103.

The Office also rejected claim 9 under 35 U.S.C. § 103(a) as being unpatentable over Busetti et al. in view of Noda et al. (U.S. Patent No. 5,137,733). Applicants respectfully submit that the combination of Busetti et al. and Noda et al. does not render the invention of claim 9 obvious. However, solely in an effort to advance prosecution, Applicants have canceled claim 9, thereby obviating the rejection.

Conclusion

Applicants respectfully submit that the remarks and amendments in this Preliminary Amendment completely respond to all of the outstanding rejections from the parent application. In view of the foregoing remarks, Applicants submit that the

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presently claimed invention is neither anticipated nor rendered obvious in view of the documents cited against the parent application.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Appendix to Amendment

A. The specification is amended as follows:

The paragraph at page 40, lines 16-24, is amended as follows:

--The results are shown in Figs. 1 and 2 wherein:

A = The product of Example [2] 5

B = The product of Example [3] 2

C = The product of Example 4

D = The product of Example [5] 3.--

B. The claims are amended as follows:

1. (ONCE AMENDED) A multiparticulate bisoprolol formulation for once-daily oral administration, [each particle] said formulation comprising at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, [surrounded by] and a polymeric coating, wherein following administration said [polymeric coating being effective to achieve] formulation produces a bisoprolol plasma concentration of not more than about 1 ng/ml for at least about three hours, and thereafter provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 12 hours following administration, [an initial lag of bisoprolol release *in vivo* of at least 4-6 hours following administration] and [thereafter maintaining] wherein said formulation maintains a therapeutic plasma [concentrations] concentration of bisoprolol for the remainder of [the] a twenty-four hour period measured from administration.

2. (CANCELED)

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3. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim] claim 1 [or 2], [which contains] comprising a pharmaceutically acceptable salt of bisoprolol.

4. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim] claim 3, wherein the bisoprolol salt is bisoprolol hemifumarate.

5. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 1, which, [has an *in vitro* dissolution profile which] when measured in a U.S. Pharmacopoeia 2 Apparatus (Paddles) in phosphate buffer at pH 6.8 at 37°C and 50 rpm, exhibits a dissolution profile substantially [corresponds] corresponding to the following:

(a) from 0% to 10% of the total bisoprolol is [released] measured after 2 hours [of measurement] in said apparatus;

(b) from 0% to 50% of the total bisoprolol is [released] measured after 4 hours [of measurement] in said apparatus; and

(c) greater than 50% of the total bisoprolol is [released] measured after 10 hours [of measurement] in said apparatus.

6. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 1, which, [has an *in vitro* dissolution profile which] when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period, exhibits a dissolution profile substantially [corresponds] corresponding to the following:

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(a) from 0% to 10% of the total bisoprolol is [released] measured after 2 hours [of measurement] in said apparatus;

(b) less than 50% of the total bisoprolol is [released] measured after 4 hours [of measurement] in said apparatus; and

(c) greater than 20% of the total bisoprolol is [released] measured after 10 hours [of measurement] in said apparatus.

7. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 1, wherein the at least two particles comprise a sealant or barrier layer [is applied to] between the core [prior to the application of] and the polymeric coating.

8. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim] claim 7, wherein the sealant or barrier layer [is selected from] comprises at least one of hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose [and] or xanthan gum.

9. (CANCELED)

10. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 1, wherein the polymeric coating [contains a major proportion of a] comprises at least one pharmaceutically acceptable film-forming polymer [which] that forms an insoluble film of low permeability and wherein said at least one polymer that forms an insoluble film of low permeability comprises from about 80 to about 100 percent of the polymers in said coating.

11. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 10, wherein the polymeric coating [contains a minor

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proportion of a] comprises at least one pharmaceutically acceptable film-forming polymer [which] that forms an insoluble film of high permeability and wherein said at least one polymer that forms an insoluble film of high permeability comprises from about 0 to about 20 percent of the polymers in said coating.

12. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim 10 or 11] claim 10, wherein the [or each polymer is] polymeric coating comprises a methacrylic acid co-polymer.

13. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim 10 or 11] claim 10, wherein the [or each polymer is] polymeric coating comprises an ammonio methacrylate co-polymer.

14. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim 12 or 13] claim 12, wherein the polymeric coating comprises a mixture of [said polymers is used] methacrylate co-polymers and ammonio methacrylate co-polymers.

15. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 1, wherein the polymeric coating comprises at least one soluble excipient [includes one or more soluble excipients so as to increase the permeability of the coating].

16. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim] claim 15, wherein the [or each] soluble excipient is [selected] chosen from [a] soluble [polymer] polymers, [a surfactant] surfactants, [an] alkali metal [salt] salts, [an] organic [acid] acids, [a sugar] sugars, and [a] sugar [alcohol] alcohols.

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17. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim 15 or 16] claim 15, wherein the soluble excipient is [selected] chosen from polyvinyl pyrrolidone, polyethylene glycol, and mannitol.

18. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any one of Claims 15-17] claim 15, wherein the soluble excipient is [used] present in an amount of from 1% to 10% by weight, based on the total dry weight of [the] polymer in the polymeric coating.

19. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim] claim 1, wherein the polymeric coating [includes] comprises one or more auxiliary agents [selected] chosen from [a filler] fillers, [a plasticiser] plasticizers, and [an] anti-foaming [agent] agents.

20. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 1, wherein the polymeric coating [polymer is coated to] produce a weight gain of from about 10% to 100% [weight gain on] to the core.

21. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 20, wherein the polymeric coating [polymer is coated to] produce a weight gain of from about 25% to 70% [weight gain on] to the core.

22. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [any preceding claim] claim 1, wherein a sealant or barrier is applied to the polymeric coating.

23. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according [Claim] claim 22, wherein the sealant or barrier [is selected from] comprises at least

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one of hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, [and] or xanthan gum.

24. (ONCE AMENDED) An oral dosage form [containing] comprising a multiparticulate bisoprolol formulation according to [any one of Claims 1-23] claim 1, which is in the form of caplets, capsules, particles for suspension [prior to dosing], sachets, or tablets.

25. (ONCE AMENDED) [An] The oral dosage form according to [Claim] claim 24, which is in the form of tablets [selected] chosen from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets, and mini-tablets.

28. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim] claim 11, wherein the [or each polymer is] polymeric coating comprises a methacrylic acid co-polymer.

29. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim] claim 11, wherein the [or each polymer is] polymeric coating comprises an ammonio methacrylate co-polymer.

30. (ONCE AMENDED) [A] The multiparticulate bisoprolol formulation according to [Claim 13] claim 11, wherein the polymeric coating comprises a mixture of [said polymers is used] methacrylate co-polymers and ammonio methacrylate co-polymers.

31. (NEW) The multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating comprises at least one polymer that dissolves in a pH-dependent manner.

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32. (NEW) The multiparticulate bisoprolol formulation according to claim 31, wherein the formulation releases bisoprolol in a manner that is dependent on the local pH of the gastrointestinal tract.

33. (NEW) The multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating comprises at least one polymer that dissolves in a pH-independent manner.

34. (NEW) The multiparticulate bisoprolol formulation according to claim 33, wherein the formulation releases bisoprolol in a manner that is independent of the local pH of the gastrointestinal tract.

35. (NEW) The multiparticulate bisoprolol formulation according to claim 1, wherein the formulation provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 6 hours following administration.

36. (NEW) The multiparticulate bisoprolol formulation according to claim 1, wherein the formulation further comprises talc.

37. (NEW) The multiparticulate bisoprolol formulation according to claim 1, wherein the formulation comprises a substantially purified enantiomer of bisoprolol.

38. (NEW) The multiparticulate bisoprolol formulation according to claim 37, wherein the substantially purified enantiomer of bisoprolol is (S)-bisoprolol.

39. (NEW) The multiparticulate bisoprolol formulation according to claim 37, wherein the substantially purified enantiomer of bisoprolol is (R)-bisoprolol.

40. (NEW) The multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating comprises at least one pharmaceutically acceptable film-forming polymer that forms an insoluble film of low permeability.

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41. (NEW) The multiparticulate bisoprolol formulation according to claim 40, wherein the polymeric coating further comprises at least one pharmaceutically acceptable film-forming polymer that forms an insoluble film of high permeability.

42. (NEW) The multiparticulate bisoprolol formulation according to claim 40, wherein the at least one pharmaceutically acceptable film-forming polymer that forms an insoluble film of low permeability is present in an amount greater than the amount of any pharmaceutically acceptable film-forming polymers that form an insoluble film of high permeability.

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